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COMMISSIONER

MEMORANDUM

To: Elaine Krueger
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From: Martha Steele

Re: Health Effects of Chlorpyrifos

Date: December 1, 1983

This memo summarizes the health effects of chlorpyrifos, and is submitted for consideration by members of the Pesticide Board Subcommittee.

Mode of Action

Chlorpyrifos is an organophosphate, a group of chemicals that inhibit cholinesterases, which are enzymes involved in transmitting nerve impulses. Symptoms of organophosphate poisoning include perspiration, salivation, muscular weakness, constriction of pupils, nausea, and chest tightness.

Chlorpyrifos is rapidly absorbed by ingestion and inhalation, and less so through the skin. Its major metabolite is 3,5,6-trichloro-2-pyridinol, which is less toxic than the parent compound. Chlorpyrifos is rapidly metabolized and excreted.

Animal Toxicity

Chlorpyrifos is moderately acutely toxic via the oral route. The oral LD50 in rats is 138-245 mg/kg. It is much less toxic by the dermal route, since the rabbit dermal LD50 is about 2000 mg/kg. The low dermal toxicity is important in considering the safety of applicators, who are often exposed by the dermal route.

Long-term feeding studies in animals have determined no-adverse-effect levels with regard to cholinesterase inhibition. Rats and dogs received chlorpyrifos in the diet for two years, and plasma and red-cell cholinesterases were periodically measured (McCollister et al, 1974). The NAS stated that "dosages of 0.1 mg/kg per day or less had no effect on plasma and red-cell cholinesterase activity in rats, whereas 0.03 mg/kg per day was the largest dose tested that had no measurable effect in dogs" (NRC, 1982, pg.43). No other adverse effects were seen.

Chlorpyrifos has not been shown to be carcinogenic. One 105 week study in mice (Warner et al, 1980) showed no increase in a variety of tumors and other lesions, such as hyperplasia. Although the study may not have used maximum tolerated doses, it was well done.

The lack of a carcinogenic effect is supported by a lack of mutagenic potential. Since cancer can be related to genetic alterations, detection of such changes is indicative that a substance may have carcinogenic potential. In the case of chlorpyrifos,the mutagenic potential of the chemical has been studied in several strains of S. typhimurium and E.coli with negative results (Poole et al, 1977; Shirasu et al,1976).

Chlorpyrifos has not been shown to be teratogenic (i.e., does not cause defects of fetal development). Deacon et al (1980) studied the teratogenic potential of chlorpyrifos in mice, and reported negative findings for this endpoint. At the highest dose only (25 mg/kg), there was severe maternal toxicity, which may have caused the fetotoxicity that was observed at this dose. The authors repeated the experiment with a maximum dose of 10 mg/kg, and no teratogenic effects were observed, despite a decrease in both plasma and red-cell cholinesterase of the maternal animals at this dose.

Some organophosphates are also neurotoxins, producing what is known as delayed neuropathy. Essentially, this involves damage to the nerve itself, occurs perhaps weeks after exposure, and is independent of any inhibition of cholinesterases. Chlorpyrifos does not appear to have the potential to produce delayed neuropathy.

Human Toxicity

There have been no long-term studies in humans. A number of field studies, where workers used a Dursban spray in insect control operations, were conducted (Ludwig et al, 1979; Eliason et al, 1969; Kenaga & Lembright, 1967). The only effect noted was a decrease in plasma cholinesterase.

Short-term clinical experiments have also been conducted. The only effect noted was plasma cholinesterase inhibition (with no clinical symptoms). The NAS stated the no-adverse-effect level for plasma and red-cell cholinesterase activity for humans is 0.03 mg/kg (NRC, 1982). The level is based on a study by Coulston et al (1972) where 0.03 mg/kg/day for 21 days had no effect on cholinesterase activity.

While chlorpyrifos can be absorbed through the skin, "prolonged exposure appears necessary for appreciable absorption to take place" (NRC, 1982, pg. 42). A number of experiments with humans exposed dermally have been conducted [Kilian et al, 1970; Pennington and Edwards, 1971; Nolan et al, 1982]. Dosages ranged from 3.1 to 31 mg/kg, in exposures varying from 12 continuous hours only, to repeated exposures (12 continuous hours/exposure) for up to four weeks. The only effect ever noted was a depression in plasma cholinesterase. This occurred in one volunteer after exposure to 3.1 mg/kg chlorpyrifos for 20 12-hour periods over four weeks (Kilian et al, 1970). Another study also showed that less than 3% of the chlorpyrifos applied to the skin was absorbed (Nolan et al, 1982).

Guidelines

The only effect seen from exposure to chlorpyrifos is cholinesterase inhibition. Plasma cholinesterase appears to be a much more sensitive indicator than red-cell cholinesterase. The significance of plasma cholinesterase inhibition is not known. Nonetheless, guidelines that have been developed are based on cholinesterase inhibition effects.

The NRC Committee on Toxicology (1978) suggested an air concentration of chlorpyrifos for submarines. They used a human no-adverse-effect level of 0.03 mg/kg (from Coulston et al, 1972), and derived an airborne concentration of 100 ug/m3 for a 70 kg man and for a 90 day continuous exposure period.

The NAS suggested an interim guideline for military housing of 10 ug/m3, not exceeding three years (NRC, 1982). A safety factor of 10 was applied to the submarine guideline, due to the more heterogenous population in military housing.

Assuming the human no-adverse-effect level of 0.03 mg/kg, the 10 ug/m3 guideline would allow the following maximum daily doses:

(70 kg x 0.03 mg/kg) = 2.1 mg total dose for 70 kg adult
(10 kg x 0.03 mg/kg) = 0.3 mg total dose for 10 kg child

A 70 kg adult breathes 20 m3 air/day, and a 10 kg child breathes 10 m3 air/day. The guideline is 10 ug chlorpyrifos/m3.

For a 70 kg adult:

$$\frac{10 \text{ ug}}{\text{m3}} \times 20 \text{ m3} = 200 \text{ ug or } 0.2 \text{ mg total dose of chlorpyrifos}$$

For a 10 kg child

$$\frac{10 \text{ ug}}{\text{m3}} \times 10 \text{ m3} = 100 \text{ ug or } 0.1 \text{ mg total dose of chlorpyrifos}$$

Thus, the margin of safety from the no-adverse-effect level is approximately 10 for a 70 kg adult, and approximately 3 for a 10 kg child. In these calculations, 100% absorption of chlorpyrifos by inhalation is assumed. Twenty-four hour exposure to the 10 ug/m3 level is also assumed.

The FAO/WHO (FAO/WHO, 1972; Vettorazzi, 1979) estimated a human no-effect-level of 0.014 mg/kg. A margin of safety of 10 was then applied to derive an acceptable daily intake (ADI) of 0.0015 mg/kg (or 1.5 ug/kg). This would translate to a 105 ug total dose/day for a 70 kg adult, and a 15 ug total dose/day for a 10 kg child. The ADI proposed by the FAO/WHO is very conservative.

The FAO/WHO no-effect-level is half the NAS level. Both levels were based on the same study (Coulston et al, 1972). In the study, several exposure regimens were tested. One involved 0.014 mg/kg/day for 28 days, and another 0.03 mg/kg/day for 21 days. No effect was observed at either dose. FAO/WHO used the former result, while NAS used the latter result; hence, the difference in no-effect-levels between the two groups.

The TLV-TWA of chlorpyrifos is 0.2 mg/m3 based on long-term feeding studies in rats and dogs and short-term studies in humans (ACGIH, 1981). One should note the usual precaution, however, that occupational standards do not consider more sensitive segments of the population, nor longer exposure periods.

SUMMARY

The only known effect of chlorpyrifos is cholinesterase inhibition. There have been a number of human experiments, both in the field and in clinical settings. Only plasma cholinesterase has been depressed, and not red-cell cholinesterase.

In animals, chlorpyrifos has low acute dermal toxicity and is moderately acutely toxic via the oral route. Adequate testing has been conducted for chronic effects, such as carcinogenicity, mutagenicity, and reproductive effects, and results have been negative.

The guideline of 10 ug/m3 suggested by the NAS is a conservative guideline and provides an adequate margin of safety to protect the public health.

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